

STATE-OF-THE-ART PAPER

The Present State of Coronary Computed Tomography Angiography

A Process in Evolution

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In the past 5 years since the introduction of 64-detector row cardiac computed tomography angiography (CCTA), there has been an exponential growth in the quantity of scientific evidence to support the feasibility of its use in the clinical evaluation of individuals with suspected coronary artery disease (CAD). Since then, there has been considerable debate as to where CCTA precisely fits in the algorithm of evaluation of individuals with suspected CAD. Proponents of CCTA contend that the quality and scope of the available evidence to date support the replacement of conventional methods of CAD evaluation by CCTA, whereas critics assert that clinical use of CCTA is not yet adequately proven and should be restricted, if used at all. Coincident with the scientific debate underlying the clinical utility of CCTA, there has developed a perception by many that the rate of growth in cardiac imaging is disproportionately high and unsustainable. In this respect, all noninvasive imaging modalities and, in particular, more newly introduced ones, have undergone a higher level of scrutiny for demonstration of clinical and economic effectiveness. We herein describe the latest available published evidence supporting the potential clinical and cost efficiency of CCTA, drawing attention not only to the significance but also the limitations of such studies. These points may trigger discussion as to what future studies will be both necessary and feasible for determining the exact role of CCTA in the workup of patients with suspected CAD. (J Am Coll Cardiol 2010;55: 957–65) © 2010 by the American College of Cardiology Foundation

Cardiac computed tomography angiography (CCTA) has emerged in recent years as a promising noninvasive anatomic imaging modality for coronary artery and cardiac structural and functional evaluation (1). Developments in computed tomography (CT) technology, driven principally by improvements in temporal resolution, spatial resolution, and volume coverage, now permit routine evaluation of the coronary arteries and cardiovascular structures with clarity. CCTA has experienced resultant rapid clinical adoption by some for assessment of patients with suspected coronary artery disease (CAD). This year, scientific guidelines for performance, interpretation, and reporting of CCTA were published that can aid the clinician-imager in the proper execution of CCTA. Nevertheless, despite the rapid growth in the scientific evidence base that has supported the formation of these guidelines, numerous evidence gaps continue to exist in this still nascent field, thus precluding

the development of practice guidelines that can endorse the proper clinical application of CCTA.

The purpose of this review is to highlight contemporary developments that have occurred in the field of CCTA that may help to bridge certain evidence gaps. We focus our discussion on issues related to diagnostic accuracy, prognostic risk stratification, cost-effectiveness, and safety.

Diagnostic Coronary Artery Evaluation by CCTA

Diagnostic accuracy of CCTA for obstructive CAD.

Since the introduction of 64-detector row CCTA in 2005, >50 studies have been published that compared the diagnostic performance of CCTA with that of invasive coronary angiography (ICA) as the reference standard. Several pooled analyses have been performed that showed the diagnostic performance of 64-detector row CCTA, with high per-patient sensitivity and specificity ranging from 91% to 99% and 74% to 96%, respectively (2–6). These early studies were uniformly retrospective in design and limited to single centers, thus possessing numerous limitations including referral bias (patients already being referred for ICA), spectrum bias (patients had a high pretest CAD likelihood and did not represent those for whom noninvasive imaging is generally performed), workup bias (overlooking patients who may have otherwise been found to have false-negative

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Abbreviations and Acronyms

CAD	= coronary artery disease
CACS	= coronary artery calcium score(s)
CCTA	= cardiac computed tomography angiography
CT	= computed tomography
ICA	= invasive coronary angiography
MPS	= myocardial perfusion scintigraphy
NPV	= negative predictive value
PPV	= positive predictive value

findings), ascertainment bias (using nonrandom samples resulting in altered results), and publication bias (emphasizing only positive results). To address many of these limitations, 3 prospective multicenter studies were recently reported that detail the diagnostic performance of CCTA in different populations (Table 1).

The purpose of these studies was to define the concordance between CCTA and a reference standard of ICA, and, thus, each of these studies was limited to patients being clinically referred for ICA. The first of these trials was the ACCURACY (Assessment by Coronary Computed

Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial, a 16-center U.S.-based study that restricted analysis to patients without known CAD undergoing CCTA before elective ICA (7). Reasons for ICA referral included stable chest pain syndrome and/or abnormal functional stress testing results. Among the 230 subjects, only 13.9% were found to have obstructive CAD at the $\geq 70\%$ stenosis threshold by quantitative coronary angiography. Although the prevalence of CAD in the ACCURACY trial cohort highlighted the imperfections of current clinical and imaging algorithms for the proper identification of individuals with obstructive CAD, it nevertheless permitted an assessment of CCTA diagnostic performance in a patient population for whom CCTA use is generally advocated. The diagnostic sensitivity, specificity, and positive predictive value (PPV) and negative predictive value (NPV) of CCTA to detect a $\geq 70\%$ stenosis in this population were 94%, 83%, 48%, and 99%, respectively. Importantly, these test characteristics were calculated reporting all vessel segments, without exclusion of patients for baseline heart rate, coronary artery calcium score (CACS), or body mass index; which is in contrast to many previous single-center studies that reported higher diagnostic performance characteristics. The area under the receiver-operator characteristic curve, which describes the discriminatory power of diagnostic testing across a wide range of cutoff values, for identification of patients with $\geq 70\%$ stenosis was 0.95, thereby definitively establishing the high diagnostic

accuracy for both detection and exclusion of obstructive coronary artery stenosis in individuals without known CAD with a low prevalence of CAD (Fig. 1).

In contrast, the 291 patients enrolled in the multicenter CORE64 (Coronary Evaluation on 64) study, encompassed an admixture of patients both with and without known CAD with baseline CACS < 600 Agatston units (8). As such, the prevalence of obstructive CAD at the 50% intraluminal stenosis threshold was higher than that observed in the ACCURACY trial, with a prevalence of 56% despite exclusion for elevated CACS of > 600 Agatston units. In the CORE64 study, the per-patient sensitivity, specificity, PPV, and NPV were 85%, 90%, 91%, and 83%, respectively. These findings are in accord with those of the ACCURACY trial because the higher prevalence of CAD resulted in predictably lower NPVs and higher PPVs. In this study population, the area under the curve was 0.91 for ICA-confirmed CAD and similar to ICA for the prediction of subsequent coronary artery revascularization.

The most recent prospective multicenter study evaluated 360 patients without known CAD presenting with both acute and stable chest pain (9). As expected, the CAD prevalence was high (68%), and diagnostic performance of CCTA revealed a per-patient sensitivity, specificity, PPV, and NPV of 99%, 64%, 86%, and 97%, respectively. In conjunction with the ACCURACY trial, the high sensitivity and NPV in individuals without known CAD highlight the ability of CCTA to detect and exclude obstructive coronary artery stenosis across wide disease prevalences, albeit with comparatively low specificity and PPVs. The latter of these diagnostic performance characteristics underscores an excessive rate of false-positive CCTA findings in which intraluminal stenosis severity by CCTA is erroneously overestimated. This fact necessitates careful consideration when using CCTA because false-positive findings may precipitate unnecessary referral for ICA. Particularly in the lower risk diagnostic population, this may result in the performance of layered noninvasive and invasive procedures for individuals who may, in fact, not have needed any testing at all.

Diagnostic accuracy of CCTA for myocardial ischemia.

Results of functional myocardial perfusion scintigraphy (MPS) have proven robust for diagnosis, risk stratification, and guidance of treatment decision making (10–21). Both large prospective, observational registries and multicenter randomized, controlled trials support a symptom benefit and potential risk reduction of revascularization for those

Table 1 Summary of Diagnostic Performance of 64-Detector Row CCTA From Prospective Multicenter Studies

	n	CAD Prevalence	Patient Type				Sensitivity	Specificity	PPV	NPV
			Stable	Unstable	No Known CAD	Known CAD				
ACCURACY (7)	230	25%	X		X		95%	83%	64%	99%
CORE64 (8)	291	56%	X		X	X	85%	90%	91%	83%
Meijboom et al. (9)	360	68%	X	X	X		99%	64%	86%	97%

CAD = coronary artery disease; CCTA = cardiac computed tomography angiography; NPV = negative predictive value; PPV = positive predictive value.

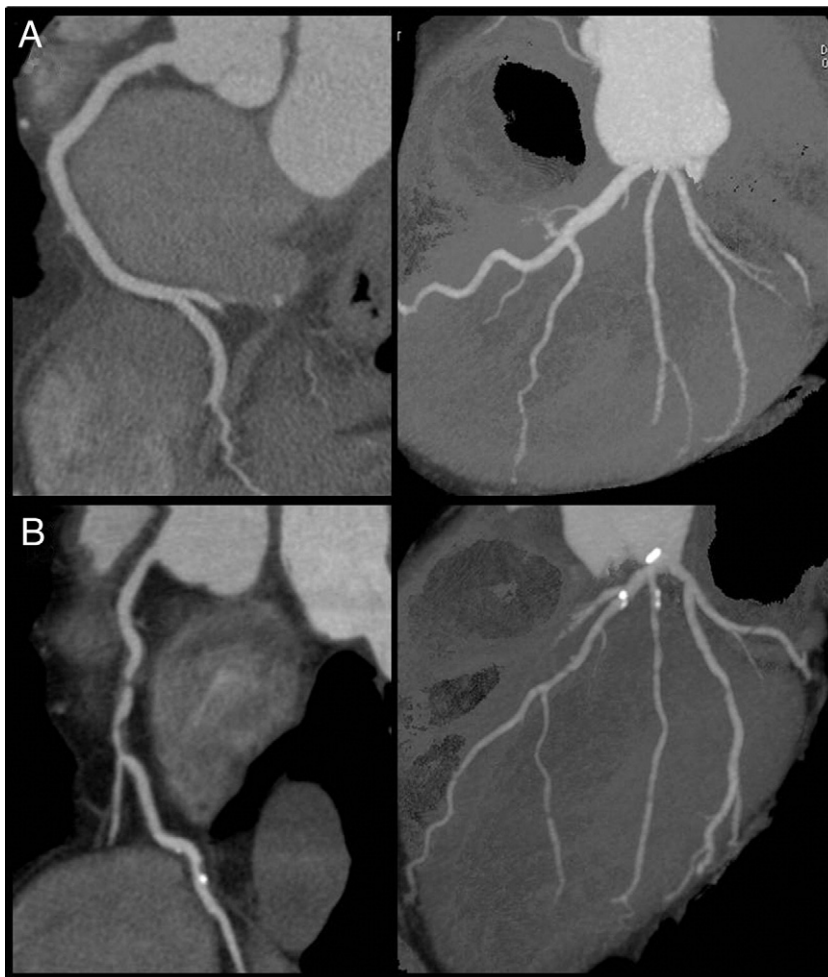


Figure 1 CCTA Examples

(A) Cardiac computed tomography angiography (CCTA) of the right coronary artery (left) and left anterior descending artery (right), which demonstrates no significant coronary artery plaque. (B) CCTA (left) and left anterior descending artery (right), which demonstrates high-grade obstructive and mild plaque, respectively.

with moderate to severe ischemia (16,17,22). The converse of this finding is also true; namely, among patients without evident extensive myocardial ischemia by MPS, an adverse CAD prognosis is higher for patients undergoing coronary revascularization than receiving medical therapy. As such, there has been an effort to determine whether CAD stenosis severity detection by CCTA successfully identifies individuals with myocardial ischemia.

In a prospective study of 78 patients undergoing sequential CCTA, MPS, and ICA, the sensitivity and NPV for CCTA to detect any perfusion defect was high (94%), although the specificity and PPV were only 64% and 63%, respectively (23). Given that increasing rates of false-positive results will reduce both specificity and PPV, these findings suggest an overestimation of CAD stenoses by CCTA. Interestingly, these findings did not reflect a failure of CCTA per se to accurately assess coronary artery stenosis because the probabilistic odds of CCTA to detect myocar-

dial ischemia were identical to those of ICA. Rather, an excessively high rate of false-positive results is seen by any method of anatomic evaluation, thus questioning the relevance of coronary artery stenosis detection by anatomic methods for identification of individuals who may most benefit from revascularization. In a similar study of 79 patients undergoing CCTA and ICA with fractional flow reserve measurements, comparable findings were observed. Although the sensitivity of CCTA by visual estimation to detect lesions with a fractional flow reserve <0.75 was high (94%), the specificity to detect such lesions was poor (40%) (24). A quantitative CCTA-based method improved diagnostic accuracy but at the loss of sensitivity; these findings were similar to those observed for quantitative coronary angiography.

A similar theme emerges from pooled analyses of studies specifically examining the association between MPS and CCTA findings (25). CCTA judged as revealing $<50\%$

stenosis at the per-patient level generally portends a normal MPS, in keeping with the high NPV of CCTA. Conversely, however, CCTA noted to reveal $\geq 50\%$ stenosis is associated with abnormal MPS only approximately half of the time (Fig. 2) (26). Collectively, these findings demonstrate that anatomic measures of stenosis severity and functional measures of myocardial perfusion provide discrete and potentially complementary information regarding CAD (i.e., anatomic detection of atherosclerosis and functional detection of ischemia). When the criterion of $\geq 50\%$ or $\geq 70\%$ stenosis has been used, a criterion now considered to be a superior standard for hemodynamic significance and guiding decisions regarding revascularization, higher PPVs of CCTA regarding ischemia by MPS have been shown (27,28).

Nevertheless, although CCTA and MPS do provide complementary information, early studies suggested methods by which CCTA plaque identification may enhance prediction of functional information, thereby lessening the ischemic gap between these 2 types of studies. Previous evaluations of CCTA relied primarily on binary measures of coronary artery stenosis severity (i.e., $\geq 50\%$ [or 70%] stenosis). Recent CCTA studies extended this categorization to a more comprehensive plaque assessment beyond intraluminal stenosis severity, including plaque location, distribution, composition, and overall burden, to determine whether these combined measures can augment the prediction of myocardial ischemia.

Lin et al. (29) evaluated 163 patients undergoing both 64-detector row CCTA and MPS. In addition to binary classification of patients with or without obstructive CAD, plaque by CCTA at the per-patient level was also graded by several scores that aimed to describe overall coronary artery plaque burden, accounting for both plaque burden and plaque location. These scores were expressed as a segment stenosis score, a segments-at-risk score, and a modified

Duke CAD score, respectively. Plaques at the per-patient level were also described by plaque composition scores, which tallied the numbers of coronary segments (based on a modified 16-segment American Heart Association model) exhibiting primarily noncalcified plaque ($>70\%$ noncalcified), mixed plaque (30% to 70% noncalcified), and calcified plaque ($<30\%$ noncalcified).

In keeping with previous studies, CCTA identification of obstructive CAD did not successfully identify individuals with abnormal MPS findings. However, measures of per-patient coronary artery plaque burden, proximity, and location, including the segment stenosis score, the segments-at-risk score, and the modified Duke CAD score, were predictive of identifying individuals with abnormal MPS findings. Increasing numbers of segments exhibiting mixed plaque similarly identified individuals with abnormal MPS findings. An extension of these findings was observed in a study of 165 patients undergoing treadmill exercise testing in which the modified Duke CAD score by CCTA successfully identified individuals with increasing severity of exercise-induced ST-segment depression as well as a decreasing Duke treadmill score (30). Notably, increasing gradations of CAD by CCTA from none to nonobstructive to obstructive also predicted a stepwise reduction in overall Bruce treadmill protocol exercise times. Collectively, these findings suggest that comprehensive assessment of coronary artery plaque by CCTA, beyond binary categorization of stenosis severity, may enhance the prediction of individuals with inducible myocardial ischemia.

Risk stratification by CCTA in individuals with stable chest pain. Of importance in the diagnostic performance of any test is its prognostic potential. The robustness of functional stress testing, by electrocardiography or imaging, to provide valuable information regarding risk stratification in a diversity of patient types explains, in large part, its popularity of use and critical importance in the evaluation of patients with suspected CAD. In contrast to the wealth of data that support the clinical effectiveness of functional stress testing, relatively few studies exist to support the prognostic implications of CCTA. This is due to the recent introduction of CT scanners capable of performing routine CCTA, which has limited the time required for accrual of cardiac events after testing. Despite the multitude of plaque characteristics that are available for identification by CCTA, early work in this field has primarily focused on the relationship of obstructive CAD to the incidence of adverse CAD prognosis.

An initial publication examined coronary artery stenosis severity in relation to the incidence of all-cause death in 1,127 patients undergoing CCTA by 16-detector row CCTA (31). At an intermediate-term follow-up of 15 months, CCTA measures of CAD severity, extent, location, and distribution were independent predictors of the risk of all-cause mortality. Both moderate ($\geq 50\%$ to 69%) and severe ($\geq 70\%$) luminal diameter stenoses revealed by CCTA were associated with a higher mortality risk com-

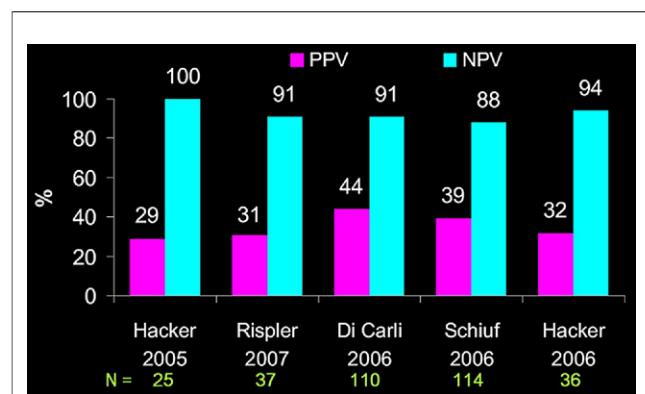


Figure 2 Relationship Between CCTA and Ischemia

Predictive value by according to 5 studies of cardiac computed tomography angiography (CCTA) to detect myocardial ischemia by myocardial perfusion scintigraphy. Reprinted, with permission, from Hachamovitch et al. (26). NPV = negative predictive value; PPV = positive predictive value.

pared with less obstructive plaques, and the risk of death increased with numbers of major epicardial vessels affected. CCTA characteristics predicting a high risk of death from a modified Duke CAD score (listed by increasing risk) included: 1) 2 segments with moderate stenosis or 1 segment with severe stenosis; 2) 3 segments with moderate stenosis, 2 segments with severe stenosis, or severe stenosis in the proximal left anterior descending artery; 3) 3 segments with severe stenosis or 2 segments with severe stenosis that included the proximal left anterior descending artery; and 4) moderate or severe left main artery stenosis, with a 15% 1.5-year mortality rate. Of equal importance, CCTA was able to accurately identify individuals with a low incidence of risk of all-cause mortality. Among 333 patients with no detectable coronary artery plaque by CCTA, the annualized death rate was 0.3%, suggesting the detection of a low-risk group.

Although long-term prognostic studies using current-generation CT scanners are as yet unavailable, studies using older generation scanners (including electron beam CCTA) have accumulated a longer accumulated experience of study. In a recent analysis of 2,538 consecutive patients without known CAD undergoing electron beam CCTA followed for 6.5 years for all-cause mortality, a higher mortality risk was identified for individuals with greater numbers of major epicardial coronary artery vessels exhibiting obstructive CAD (32). In comparison with patients without CAD, the mortality incidence increased 2- to 3-fold. Even among individuals without evident obstructive CAD, the presence of nonobstructive CAD in all 3 major coronary vessels conferred a significantly increased risk of mortality. Importantly, for patients without evident CAD, the annualized mortality rate was 0.3% in this follow-up of nearly 7 years, suggesting that the “warranty” period of a normal CCTA may be extensive. Furthermore, risk prediction by CT-identified plaque was independent of and additive to traditional CAD risk factor scoring and CACS.

CCTA has also been evaluated for its ability to identify individuals at risk of other major adverse cardiovascular events. In the largest of these studies, 1,256 patients undergoing 64-detector row CCTA were studied for all-cause death in relation to CAD severity. Individuals with obstructive CAD experienced significantly higher rates of severe major adverse cardiovascular events (odds ratio: 17.3, 95% confidence interval [CI]: 3.6 to 82.5, $p < 0.001$), as defined as cardiac death, myocardial infarction, or unstable angina requiring hospitalization. Conversely, those individuals without obstructive CAD by CCTA experienced major adverse cardiovascular events at a substantially lower rate than would have been predicted by traditional Framingham risk factor scoring.

Pooled analyses of studies of individuals undergoing CCTA indicate an inordinately high annualized event rate (11.1%, 95% CI: 5.1% to 25.5%) for those with obstructive CAD, which is by and large higher than that observed for individuals with abnormal perfusion shown by MPS (6.2%,

95% CI: 5.9% to 6.5%) or inducible wall motion abnormalities by stress echocardiography (7.5%, 95% CI: 5% to 13.4%), albeit with overlapping CIs (33,34). These observations have prompted the question as to the relative prognostic risk stratification proffered by CCTA compared with functional stress testing. Further, whether CCTA plaque characteristics predict future adverse CAD outcomes in a manner that is equivalent to or synergistic with that of perfusion or wall motion findings has also been raised. To date, only 2 studies have been performed to offer early data with respect to these issues.

In the first of these studies, individuals undergoing CCTA for CAD evaluation ($n = 1,132$) were compared with propensity score-matched outpatients ($n = 7,849$) referred for MPS, for a primary end point of all-cause death (35). Similar 2-year survival rates after CCTA and MPS were noted (97% for both). In a comparison of CCTA findings as graded by a modified Duke CAD index versus the percentage of ischemic myocardium by single-photon emission CT, the annual mortality rates predicted by CCTA were directly proportional to the percentage of ischemic myocardium by MPS, ranging from 0.2% to 11% for CCTA and from 0% to 12% for MPS. These findings suggest that the prognostic potential of CCTA is similar to that of perfusion testing. Although the range of values for low to high risk was similar, a more gradual increase in risk was noted for CCTA in patients with less extensive CAD. Because CCTA is capable of identifying nonobstructive CAD for which functional MPS findings may be expected to be normal, future prospective studies are necessary to examine the relationship of nonobstructive plaque identification to adverse CAD events for further refinement of risk assessment on the lower ends of the risk spectrum.

A more recent study of 541 patients prospectively undergoing both CCTA and MPS examined the relative prognostic potential of CCTA CAD detection and MPS perfusion abnormalities in individuals with suspected CAD (36). During a 2-year follow-up, annualized mortality and nonfatal myocardial infarction rates were higher for patients with obstructive CAD compared with patients with none or mild CAD (4.8% and 1.8%, respectively), findings similar for patients with abnormal versus normal myocardial perfusion (3.8% vs. 1.1%, respectively). Survival analyses demonstrated comparable risk stratification for anatomic CAD findings by CCTA and functional perfusion by MPS. Anatomic and functional measures were synergistic for the prediction of death or myocardial infarction. In addition, plaque composition seemed to be important for predicting outcomes because individuals with ≥ 2 noncalcified plaques, ≥ 3 mixed plaques, and ≥ 4 calcified plaques experienced higher rates of death and MI than those with none.

These proof-of-principle studies will require corroboration in other centers and in different patient cohorts. Further, direct comparison of CCTA with MPS for prognostic risk stratification in individuals undergoing either test has to date not been performed. Before CCTA is widely

accepted as possessing equivalent or superior abilities for risk stratification, head-to-head evaluations will likely be required using randomized, controlled trials, several of which have been proposed but not yet initiated.

Use of CCTA in the evaluation of acute chest pain. Almost 6 million individuals are evaluated each year for acute chest pain in the emergency department (34). Despite standardized protocols and high vigilance, between 2% and 6% of patients are erroneously discharged with missed myocardial infarction (37). Proponents of CCTA advocate its potential usefulness in this patient subgroup, highlighting the NPV of CCTA to successfully identify individuals in whom no obstructive CAD exists and who have a favorable prognosis.

A single-center, randomized study of 197 individuals presenting with acute chest pain to the emergency department compared a CCTA-based diagnostic evaluation strategy with standard-of-care algorithms that used MPS (38). In contrast to individuals undergoing standard-of-care assessment, individuals undergoing CCTA experienced reduced diagnostic time in the emergency department (3.4 and 15.0 h, respectively; $p < 0.01$) and fewer repeat evaluations for chest pain. These findings translated to lower costs for a CCTA-based evaluation by almost \$300 per patient. In 6-month and 2-year follow-up, no adverse CAD events occurred in discharged individuals by either a CCTA- or standard-of-care-based evaluation (G. Raff, personal communication, June 2009).

In a related study, 368 patients presenting to the emergency department with acute chest pain underwent 64-slice CCTA after initially negative findings on troponin measurements and electrocardiograms (39). The caring physician was blinded to the CCTA results. One half of the study patients had no evidence of CAD by CCTA, with an NPV of 100% for acute coronary syndrome in a 6-month follow-up. By contrast, the presence of any plaque by CCTA had 100% sensitivity for acute coronary syndrome detection, although the specificity for acute coronary syndrome detection was low (54%). Specificity for acute coronary syndrome detection was improved by restriction of CAD to those with $\geq 50\%$ stenosis by CCTA, findings, which were incremental to thrombolysis in myocardial infarction risk scores.

In aggregate, the current data on CCTA for acute chest pain suggest that in appropriate populations, CCTA may be useful as a successful triage tool that may allow safe early discharge of low-risk patients. On the other hand, the presence of nonobstructive coronary artery plaque portends a low but nonzero risk, congruent with the data observed in the stable chest pain population, and is therefore an imperfect stand-alone instrument for triaging individuals with possible acute coronary syndrome. Although these early data are favorable, further study is still needed in larger cohorts to verify the safety and effectiveness of a CCTA-based evaluation of acute chest pain patients.

Cost-efficiency and resource utilization after CCTA. At present, the potential clinical utility of CCTA is not

uniformly recognized by third-party payers, with private payer coverage of CCTA for CAD evaluation existing in approximately 50% of U.S. plans. Concerns of unchecked growth for CCTA have also been expressed by the Centers for Medicare and Medicaid Services in a proposed National Coverage Determination for CCTA that called for the answer to 3 questions to appraise the value of CCTA (40). These 3 questions, which deal with diagnostic test accuracy, resource utilization, and improvement in patient-centered health outcomes, were reinforced by the Medicare Evidence Development and Coverage Advisory Committee, with input from the National Heart, Lung, and Blood Institute, which prioritized the need to answer the question: how cost-effective is CCTA (41)?

Given the shorter clinical experience with CCTA compared with other modalities such as MPS, relatively little evidence is as yet available to describe the cost-effectiveness of CCTA. Early evaluations of the economic implications of a CCTA-based strategy have relied primarily on single-center “back-of-the-envelope” calculations of costs or decision analytic models whose findings are largely driven by measures of test sensitivity and specificity.

One recent multicenter study related total health care and CAD-related costs to downstream CAD hospitalization outpatient visits, acute myocardial infarction and new-onset angina in 8,235 matched low-risk individuals undergoing CCTA or MPS (42). In a 1-year follow-up, adjusted CAD costs were 25.9% lower in individuals undergoing CCTA compared with MPS, by an average of \$1,075 per patient. These differences were driven, in part, by the lower likelihood of undergoing coronary revascularization. Despite this, rates of myocardial infarction and CAD-related hospitalization were similar, and rates of new-onset angina in individuals undergoing CCTA were lower than those reported for MPS. These findings were extended in a similar study of 9,690 matched intermediate-risk individuals undergoing CCTA or MPS (43). In a 9-month follow-up, adjusted total and CAD-related costs were one third lower for individuals after CCTA compared with MPS by an average of \$467 per patient. Rates of new CAD medications and coronary revascularization were similar in CCTA and MPS patients, and the cost differences were explained in part due to methods of downstream testing. Individuals evaluated by CCTA were more likely to undergo follow-up testing with MPS, whereas MPS individuals were more likely to undergo downstream testing by ICA. Despite lower costs for CCTA, no differences were observed for CAD events, including CAD hospitalizations, CAD outpatient visits, myocardial infarction, or new-onset angina.

Although these findings are provocative, they are far from definitive. The aforementioned studies used administrative claims data, and, thus, clinical results of CCTA or MPS as well as symptom data are lacking. The deficiency of this important clinical information prevents ascertainment of whether the increased costs noted in the MPS group were, in fact, appropriate. In addition, the nonrandomized nature

of the individuals undergoing CCTA or MPS, despite careful statistical matching techniques, may be beset by residual confounders. Further, these analyses were performed using 2005 and 2006 claims data, at a time when clinical use of 64-detector row CCTA was in its inception. The increased rates of ICA after MPS may simply reflect the unavailability of CCTA to those patients at that time. **Safety.** Performance of CCTA results in non-negligible doses of ionizing radiation, and this has been a criticism of its use. Traditional measures of radiation dosimetry by electrocardiogram-gated CCTA have used the use of an average conversion coefficient ($0.014 \text{ mSv}\cdot\text{mGy}^{-1}\cdot\text{cm}^{-1}$) to estimate the effective radiation dose from the scanner-reported dose-length product; the millisievert (mSv) unit is typically used for doses (44). Although radiation doses from MPS, ICA, and nonelectrocardiogram-gated noncardiac CT are generally straightforward in their measurements, the radiation dose of CCTA is highly variable and substantially depends on the image acquisition parameters.

Among the numerous methods of performing CCTA, radiation doses can vary by an order of magnitude, and in practice, these variations are similarly observed. In PROTECTION I (Prospective Multicenter Study on Radiation Dose Estimates of Cardiac CT Angiography in Daily Practice), 120 sites reported radiation dose estimates from CCTA (45). The average radiation dose conferred by CCTA was 12 mSv, or approximately 4 times that derived from the annual background radiation from radon. Although this dose compares favorably with MPS, it is nevertheless twice the amount of radiation associated with a diagnostic ICA. Further, the variation of dose at sites experienced in performing CCTA in PROTECTION I was wide, and ranged from 4 to nearly 30 mSv.

In an effort to minimize radiation dose from CCTA, numerous methods for dose reduction have been developed. These include automated tube current modulation, electrocardiographic modulation, prospective axial triggering, reduced tube voltage, and iterative reconstruction techniques.

The combination of these techniques can result in more than a 90% radiation dose reduction to $<1 \text{ mSv}$ (46). Nevertheless, the penetration of these techniques into widespread clinical practice outside of specialized centers has not yet occurred, and radiation dose associated with CCTA remains excessively high. A recent multicenter, single-state registry, reflecting real-world practice, reported unaffected doses of 25 mSv with CCTA (47). Educational interventions to these sites reduced radiation by almost 50%, suggesting that instruction and implementation of radiation techniques can effectively lower the radiation dose and potentially improve patient safety.

Generalizability. Although study of CCTA has been abundant since the introduction of 64-detector row CCTA scanners in 2005, the generalized applicability of these observations remains to be seen. CCTA studies have, to date, been largely performed by centers with expertise in image acquisition, reconstruction, and interpretation. Further, studies of CCTA have generally limited inclusion of patients for whom CCTA performance would be most likely successful. The ability of CCTA to be commonly applied in subjects with high CACS, irregular heart rhythms, or obese individuals can result in significant artifacts related to beam hardening, misregistration, and image noise, respectively. Whether CCTA can be routinely performed in such subjects remains to be determined, but diagnostic performance will likely be less robust than that previously reported for individuals without these characteristics.

Conclusions

The Irish playwright George Bernard Shaw once wrote, “New opinions often appear first as jokes and fancies, then as blasphemies and treason, then as questions open to discussion, and finally as established truths” (48). Primarily over the past 3 years, the profusion of scientific evidence related to CCTA has permitted evolution of the field to the

Table 2 CCTA-Related Issue and Pro and Con Argument		
CCTA Diagnostic Test Characteristic	Pro	Con
Diagnosis of obstructive CAD	CCTA possesses a high NPV for identification of individuals in whom no further testing is warranted.	CCTA possesses high rates of false positive findings, which will lead to unnecessary catheterization and revascularization.
Anatomic diagnosis of CAD	Most individuals undergoing imaging do not have significant CAD and, thus, a test with high NPV is most useful.	Ischemia-guided management is more proven than anatomy-guided management.
Detection of subclinical atherosclerosis	CCTA diagnoses individuals with subclinical atherosclerosis, which offers the opportunity to initiate primary prevention of future CAD events.	Most individuals diagnosed by CCTA with subclinical atherosclerosis should already be receiving medical therapy. Further CCTA diagnosis may simply represent lead-time bias for which no intervention is necessary or useful.
Prognosis	CCTA plaque characterization for prognostic risk assessment is as effective and is synergistic to stress imaging findings.	Functional stress testing with or without imaging is robust for risk stratification.
Resource utilization	CCTA can act as an effective gatekeeper to cardiac catheterization, thereby reducing costs.	CCTA will simply serve as an add-on test rather than as a stand-alone test, thereby increasing costs.
Safety	CCTA exposes a patient to less radiation than other tests, including nuclear stress testing and invasive angiography.	CCTA exposes a patient to excessive radiation.

CAD = coronary artery disease; CCTA = cardiac computed tomography angiography; NPV = negative predictive value.

point of raising questions, most of which remain open to discussion. In the past year alone, considerable discussion occurred regarding the widespread use of CCTA in the evaluation of patients with suspected CAD. Interestingly, the same available evidence often evokes directly contrary interpretations from proponents and critics of CCTA (Table 2).

The reasons underlying this debate stem not only from differences in scientific opinion, but also under a backdrop of spiraling health care costs and disproportionate growth in noninvasive imaging. In this regard, newly introduced technologies such as CCTA have experienced a “raising of the bar” of medical evidence required to either prove or disprove their clinical and economic effectiveness. Although this standard of evidence development has not been a historical mandate for other imaging methods, it will nevertheless be required for CCTA in the current budget-neutral health care environment that stresses comparative effectiveness against established methods of CAD evaluation.

What, then, is the current and future state of CCTA? In our opinion, the diagnostic accuracy of CCTA has already been definitively established. By well-performed prospective, multicenter studies, CCTA is an accurate diagnostic modality with superior diagnostic accuracy to detect and exclude anatomically obstructive CAD. The exclusion of CAD seems to offer immediate clinical usefulness and is likely to reduce the need for subsequent resource utilization. However, improvements are still necessary to reduce overestimation of CAD severity. With newer generation CT scanners, this will be a process of evolution.

Nevertheless, the ability of CCTA, beyond conventional methods of CAD evaluation, to predict patient-centered outcomes and to invoke appropriate medical or invasive treatment and do so safely and in a cost-effective manner has yet to be determined. The future of CCTA will lie in the answers to these questions, which will depend on the type of high-quality evidence typically only derived from large, well-designed, randomized, controlled trials.

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